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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/18/04, 6/6/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communications filed on 11/18/2004 and 6/6/2005. The amendment filed 6/6/2005 is acknowledged. The amendment has been entered. Claims 1-16 are currently pending in the application and are addressed herein.

Specification

The amendment filed 11/18/2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the 46 genes that are dispensable for viral replication that applicants have added to the paragraph beginning on page 4, lines 26 of the specification.

Applicants assert that the amendment is not new matter because the specification indicates that the Roizman articles (PNAS 1996) has been incorporated by reference (See page 5 of the communication received on 11/18/2004).

Applicants are respectfully reminded that MPEP § 608.01(p) indicates:

> "An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. Ape. 1966). An application for a patent when filed may incorporate 'essential material' by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. 'Essential material' is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates 'essential material' by reference, or (4) a foreign application. Nonessential subject matter may be incorporated by reference to (1) patents or

> applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, aperients and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art."

In the instant case, the material which has been added to the specification is considered "essential material" because it is necessary to describe the claimed invention. It is noted that claim 5 comprises the specific essential material that has been added to the specification. Since the new material added to the specification is "essential material" it may not be incorporated by reference to a non-patent publication as indicated above (See MPEP § 608.01(p)). Therefore, the new material is new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, second paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-4 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record (see the Office Action mailed on 6/15/2004) which are reiterated below for convenience.

Claim 15 is drawn to the method of any of claims 1-4 wherein the HSV genome comprises an insertion of an expressible non-natural protein coding sequence... It is noted that the specification does not define the metes and bounds of the term "non-natural protein". As such it is unclear what exactly is a non-natural protein. For instance, it is unclear if a non-natural

protein is one that is not found in the wild-type HSV genome, or if it encompasses encoding a protein made of "non-natural" amino acids, or if it means something completely different than these two possibilities. It is noted that claims 1-4 are independent claims from which claim 15 depends. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected for encompassing "non-natural protein".

Claim Rejections - 35 USC § 112, 1st paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record (see the Office Action mailed on 6/15/2004), which are reiterated below for convenience. **This is a new matter rejection.**

5. Claim 5 is drawn to the method of claim 1, 2, 3, or 4 wherein the modified HSV genome further comprises deletion of a gene selected from a large group (see claim 5). However, looking to the specification for support, it is clear that claim 5 encompasses genes that were not disclosed in the originally filed specification. Specifically, the Examiner can only find support in the originally filed specification for the following genes: UL16, UL24, UL40, UL41, UL55, UL56,

alpha22, US4, US8 and US11. Support cannot be found for the other genes. The Applicants are asked to specifically identify where, by page and line number, support for the other genes can be found.

6. Claim 15 is drawn to the method of any of claims 1-4 wherein the HSV genome comprises an insertion of an expressible non-natural protein coding sequence... Looking to the specification, support for an HSV vector comprising an insertion of an expressible non-natural protein cannot be found. It is noted that claims 1-4 are independent claims from which claims 5 and 15 depend. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected for encompassing the limitations for which there insufficient support found in the specification.

7. Claims 1-4 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record (see the Office Action mailed on 6/15/2004), which are reiterated below for convenience. **This is a written description rejection.**

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between

function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

The instant claims are drawn to a method of treatment (claims 1-4) wherein an HSV vector comprising an insertion of an expressible non-natural protein coding sequence (claim 15) is administered to a subject having cancer. It is noted that the claims encompass encoding any protein that could be considered "non-natural". However, as indicated above, the term "non-natural protein" has not been defined in the specification. Therefore the claims encompass a myriad of proteins however the specification has not disclosed a single species of this large genus of proteins. There is no indication of the any "non-natural protein" by name or by sequence. Furthermore, applicants have not identified any structural characteristics common to all species of the genus. As such the specification has not adequately described a representative number of non-natural proteins encompassed by the claims.

It is noted that claims 1-4 are independent claims from which claim 15 depends. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected for encompassing "non-natural protein".

Additionally, claims 1-4 and 15 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement—in view of the written description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As indicated above, the claims encompass a genus of molecules (specifically "non-natural proteins") which re not adequately described in the

specification. Since the specification has not adequately describe the "non-natural proteins" encompassed by the claims, one of skill in the art would not know how to make/use the invention without performing an undue amount of additional experimentation.

8. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for reducing tumor mass by directly injecting an HSV that expresses only one gamma(1)34.5 gene product into a tumor in an amount effective to reduce the mass of said tumor;

does not reasonably provide enablement for treatment in an individual via any route of administration other than direct injection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims, for the reasons of record, which are reiterated below for convenience.

The following factors have been determined by the courts to be critical in determining whether a claimed invention is enabled (See In re Wands 8 USPQ 2d 1400, Fed. Cir. 1988).

The nature of the invention: The instant claims are drawn to a method for reducing tumor mass in an "individual" comprising administering an amount of recombinant Herpes simplex virus (HSV) wherein said HSV genome comprises a modification of an inverted repeat region such that one $\gamma_1$34.5 gene remains intact and where in said amount of HSV is being effective to reduce tumor mass. Thus, the nature of the invention is a therapeutic use of

attenuated HSV virus for treating tumors and generally falls in the realm of gene therapy, and specifically encompasses oncolytic virotherapy.

The state of the prior art and the predictability or unpredictability of the art: At the time of filing, the relevant art considered gene therapy as a whole to be extremely unpredictable. Efficacious, predictable modes of delivery that would provide efficient delivery and expression of genes encoding the protein in the target cells had not been developed. Regarding the specific delivery of therapeutic viruses to targeted cells, **Verma et al.,** (1997) states that delivery is the "Achilles heel", and indicates, "[t]he use of viruses is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses" (pg. 293, col. 3, parag. 1). **Chamber** et al., (1995) previously attributed the greater survival benefit for glioma-bearing mice treated with a $\gamma_1$34.5 mutant in which the 34.5 gene is interrupted by a stop codon (R4009) rather than by deletion (R3616) due to the low level of stop codon suppression in R4009 allowing for enough viral replication so as to effectively destroy tumor cells, yet not multiply to a level where it can cause encephalitis and taught that the "key to the development of effective oncolytic viruses may well depend on precise control of the expression of the $\gamma_1$34.5 gene" and that "this observation may be exploited to construct still more effective viruses" (page 1415, left column). **Advani** (1998) teaches that "While attenuated herpes viruses alone have not been tested in humans, the available data in experimental animals do not predict a high cure rate (page 162, left column) and that "infection alone produced few cures and the majority of infected tumors either grew more slowly or outpaced cell destruction" (page 162, top right column).

Crystal (1995) has previously recited that "human are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (page 409, bottom, left column). Without an art recognized nexus between the results obtained in animal models and the results which the skilled artisan would reasonably expect to see in humans, the results of applicants animal model data are difficult or impossible to interpret.

Specifically regarding the use of nude mice as human cancer models, Trisha **Gura** teaches in her article titled "Systems for identifying new drugs are often faulty" (Science, 1997; 278:1041-1042),

> "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does." (See p. 1041, first column)

Gura also teaches, "xenografts tumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues for example. Thus, drugs tested in the xenografts appeared effective, but worked poorly in humans." (See p. 1041, column 2).

Furthermore, **Kerbel** teaches (see "What is the optimal rodent model for anti-tumor drug therapy?" Cancer and Metastasis Reviews Vol. 17:301-304; 1999), "A recurring problem with the use of present models of transplantable tumors is that they frequently respond to anti-cancer drugs or other therapies which then show no activity in humans." (See p. 301, first column). Kerbel indicates a number of specific problems with the mouse model, including (i) concentrations of drugs are used at the maximum tolerated doses for mice, not humans—it turns out that the maximum tolerated dose for mice is often significantly greater than it is for man (see

p.301, first column); (ii) most transplanted tumors are very fast growing—drugs are often designed to target rapidly dividing cells; however, natural human tumors often grow much slower. Therefore, the transplanted tumors can show an "exaggerated" response to a drug (see p. 301, second column); and (iii) the response to therapy of a single 'primary' growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases. Regarding (iii), Kerbel teaches, "Clearly this is not representative of most clinical treatment situations in which distant metastases are the target of systemic therapy, and not the primary tumor, which is generally dealt with using surgery." (See p. 302, column 1).

Additionally, the claims encompass treating any type of tumor by any route of administration that results in one or more tumor cells infected with the HSV, however, this does not limit the route of administration to direct delivery to the tumor. Rather the claims still encompass any route of administration. Therefore, the claims encompass treating CNS tumors, such as glioblastomas, by administering the HSV intravenously, subcutaneously, etc. Clearly systemic administration of the HSV (such as by intramuscular, intravenous, or subtaneous administration) would have no efficacy against glioblastoma, wherein the blood-brain barrier restricts entry of 120nm HSV particles into the brain (**Muldoon** et al. Am. Journ. Pathol. 147(6):1840-1851, 1995).

The above references acknowledge the usefulness of gene therapy for the treatment of cancer and other diseases in the future, however, they also illustrate that there are numerous obstacles that the specification would need to overcome.

The breadth of the claims and the amount of direction or guidance presented in the specification and the presence or absence of working examples:

As such, the disclosed claims are very broad and read on killing any type of tumor by delivering the attenuated HSV by any route to an individual. Clearly, systemic administration of an attenuated oncolytic herpesvirus by intramuscular injection will have little or no efficacy against a glioblastoma, wherein the blood brain barrier restricts entry into the brain of 120 nm HSV particles (**Muldoon** et al., 1995). Furthermore, there is a lack of reference between the in vivo nude mouse model data presented by applicants and results which skilled artisan would expect in humans. That is, there is no example or guidance in the specification that would indicate or guide the skilled practitioner on modifying the treatment of the nude mouse to a human that has a functional immune system. Without guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to treat glioblastoma, prostate adenocarcinoma and hepatoma in the individual.

The quantity of experimentation: To attempt to practice the claimed invention in humans, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the art, the prior art (as indicated above), also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the specification and the prior art, one of skilled in the art would resort to trial and error experimentation to navigate the obstacles to practicing the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. The

amount of experimentation required to practice the claimed invention embodiments would necessitate undue experimentation on the part of one skilled in the art.

In conclusion, given the nature of the invention, the state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the full scope of the claims is very high and is in fact undue.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-5, 7, 9-12 an 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Advani (1997; Int. Journ. Oncol. Rad. Biol. Phys) or alternatively Advani (Feb. 1998; Gene Therapy) (both previously cited) for the reasons of record (see the Office Action mailed on 6/15/2004), which are reiterated below for convenience.

The instant claims are drawn to a method for reducing tumor mass by administering an attenuated HSV to a subject having cancer wherein the HSV genome has been modified in an inverted repeat region such that the HSV has only one active gamma(1)34.5 gene, wherein the HSV is administered in an amount effective to reduce tumor mass. It is noted that the claims

explicitly encompass administering HSV R7020, and the claims explicitly encompass administering the HSV to CNS tumors.

Advani (1997) is an abstract that clearly teaches "Human U-87MG glioma cells were grown in the hind limb of athymic mice... and infected with... [HSV] R7020... the tumors were harvested... 14 days after viral injection." Furthermore, Advani teaches, "Herein we demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas." (emphasis added). Therefore, Advani (1997) clearly anticipates the instant claims as they encompass a method for reducing tumor mass comprising direct delivery of the attenuated HSV to the tumor.

Similarly, Advani (1998) also teaches the same data with more detail, as it is a complete journal article rather than an abstract. Advani (1998) teaches a number of different experiments wherein HSV R3616 is directly administered to human glioma xenografts in nude mice by itself, and in combination with other agents (e.g., see Fig.1, Fig. 2). The injected tumors were allowed to grow and then there volume was measured at different time points (Figs 1 and 2). Avani specifically teaches, "the experiment was repeated with R7020, another genetically engineered attenuated virus" (see p. 161, bottom of second column), indicating that the R7020 was also injected into glioma xenografts in a nude mouse model and tumor volume was measured at certain time points.

Applicants have previously argued that the references do not teach that method results in a reduction of tumor mass, as required by the claims. Specifically, Applicants argued,

> "Advani 1997 and 1998 disclose the same data as found in Figure 3 of Advani 1998, but neither reference discloses that the R7020 virus is able to kill tumor cells at a rate that is

> greater than the tumor is able to grow which is necessary to result in reduced tumor mass. Because anticipation requires that every limitation of the claims be found in the cited art, neither... the Advani references can anticipate the claimed invention and the rejections must be withdrawn."
> (See response filed 7/19/02).

However, it appears that both Advani references teach a method wherein HSV R7020 is administered to an animal having a CNS tumor by directly injecting the HSV into the tumor. It also appears that the injected tumors were analyzed (i.e. volume was measured) up to (at least) 14 days after injection of the HSV. It is acknowledged that the references do not explicitly teach that the administration of HSV R7020 resulted in a reduction of tumor mass. However, the references do teach all of the steps using all of the claimed materials. As such, the method taught by Advani (1997) and Advani (1998) would inherently result in the reduction of tumor mass.

It is noted that MPEP 2112 states,

> "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. 'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.' In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983)... The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)... 'In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.' Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)"

Additionally, MPEP 2112.02 states,

> "Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986)"

In the instant case, the prior art "device" is the HSV R7020 and in its normal and usual operation would necessarily perform the method claimed. Therefore, the instant claims are clearly anticipated by Advani (1997) and separately by Advani (1998).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Advani (1997; Int. Journ. Oncol. Rad. Biol. Phys) in view of Carroll et al. (Ann. Surg. 1996); or alternatively Advani (Feb. 1998; Gene Therapy) in view of Carroll et al. (Ann. Surg. 1996) for the reasons of record (see the Office Action mailed on 6/15/2004), which are reiterated below for convenience.

Advani (1997) and Advani (1998) both, separately teach a method for reducing tumor mass as previously indicated (see above rejection).

Neither Advani (1997) or Advani (1998) teach that the attenuated HSV virus could be used to treat a non-CNS tumor.

Carroll teaches treatment of non-CNS tumor using an attenuated HSV (hrR3). Specifically, Carroll teaches a method for treating colon carcinoma liver metastasis by administering an attenuated HSV directly to the tumor (e.g., see abstract).

Therefore, it would he been prima facie obvious at the time of invention that the method taught by Advani (1997) or Advani (1998) would have also been able to treat a non-CNS tumor such as a colon carcinoma liver metastasis in an animal or human, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the method Advani (either 1997 or 1998) to treat a non-CNS cancer because Carroll teaches that attenuated HSVs can be used to treat non-CNS-type tumors.

Response to Arguments

Applicant's arguments filed 11/18/2004 have been fully considered but they are not persuasive.

With respect to the rejection of claims under 35 USC 112, 2nd paragraph, Applicants argue that page 5, lines 6-10, of the specification states, "viruses useful in the practice of the present invention may have additional alterations in their genome that may include insertion of expressible non-natural protein encoding sequences under the control of herpes simplex virus promoters that in turn permits the sequence to be regulated as an α, β or γ class of herpes simplex virus genes that are well known in the art." Applicants assert that in this context, it would be clear to one of skill in the art that "non-natural protein" is a protein encoded by an inserted sequence that is expressed from a herpes simplex virus promoter from which it is not normally, i.e., naturally, expressed. Furthermore, Applicants contend that even if the line between natural and non-natural proteins were not defined clearly in the specification, claims 1-4, each of which embraces proteins on both sides of the line, would not be indefinite.

In response, the disclosure of page 5, lines 6-10 of the specification is acknowledged by the Examiner. However, this disclosure does not define "non-natural protein". The indicated disclosure merely indicates that the "non-natural protein" is expressed by the virus, without providing a definition of what the "non-natural protein" is. Therefore, the term "non-natural protein" is indefinite. Furthermore, claims 1-4 encompass "non-natural protein", as acknowledged by Applicants in the response filed 11/18/2004. Since the claims encompass the indefinite term, the claims are appropriately rejected under 35 USC 112, 2nd paragraph, regardless if they also encompass non-indefinite embodiments.

With respect to the rejection of claims under 35 USC 112, 1st paragraph for comprising new matter, Applicants argue that the subject matter that has been identified as new matter is

matter that was present in an article that the specification has incorporated by reference (Roizman et al. PNAS 1996). Applicants assert that the specification has been amended to recite the matter which is identified as new matter, and as such, the rejection should be withdrawn. Applicants also assert that none of claims 1-4 explicitly recite the limitations which are considered new matter, rather, the claims merely encompass the limitations considered new matter.

In response, Applicants are respectfully reminded that MPEP § 608.01(p) indicates:

> "An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. Ape. 1966). An application for a patent when filed may incorporate 'essential material' by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. 'Essential material' is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates 'essential material' by reference, or (4) a foreign application. Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, aperients and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art."

In the instant case, the material which has been added to the specification is considered "essential material" because it is necessary to describe the claimed invention. Since the new material added to the specification is "essential material" it may not be incorporated by reference to a non-patent publication as indicated above (See MPEP § 608.01(p)). Therefore, the new material is new matter. Furthermore, since claim 5 explicitly recites the genes which are considered new matter, the rejection is appropriate and the rejection is not withdrawn.

Furthermore, it is respectfully pointed out that claims 1-4 are independent claims that claim 5 depends from. Therefore, claims 1-4 must encompass all of the embodiments of claim 5. Since claims 1-4 encompass limitations that are explicitly claimed in claim 5, the rejection of claims 1-4 is appropriate and the rejection is not withdrawn.

With respect to the rejection of claims under 35 USC 112, 1st paragraph for an insufficient written description of the "non-natural" proteins encompassed by the claims, as well as the lack of an enabling disclosure for making and using the "non-natural" proteins, Applicants argue that one of ordinary skill in the art would recognize that "non-natural protein" is a protein encoded by a sequence that is expressed from an HSV promoter from which it is not normally expressed. Applicants also assert that which is well known in the art need not, and is preferably not recited in the specification. Applicants also contend that the rejection of claims 1-4 is inappropriate because they only encompass, without explicitly claiming "non-natural protein".

In response, although one of ordinary skill in the art may recognize that a non-natural protein, as it pertains to the instant invention, is a protein encoded by a sequence that is expressed from an HSV promoter from which it is not normally expressed, this does not provide a sufficient description such that one of skill in the art would recognize which proteins are "non-natural proteins". It is acknowledged that the specification is not required to recite that which is well known in the art. However, in the instant case, the claims encompass a myriad of different proteins; however, the specification has not provided a sufficient description of the "non-natural proteins" encompassed by the claims such that one of skill in the art would be able to recognize which proteins are non-natural proteins. Since the claims encompass embodiments which have

not been adequately described in the specification, one of skill in the art would not know how to make and/or use the therapeutic HSVs encompassed by the claims. Furthermore, it is respectfully pointed out that claims 1-4 are independent claims that claim 15 depends from. Therefore, claims 1-4 must encompass all of the embodiments of claim 15. Since claims 1-4 encompass limitations that are explicitly claimed in claim 15, the rejection of claims 1-4 is appropriate and the rejection is not withdrawn.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (scope of enablement), Applicants argue that the Examiner has acknowledged that the level of skill in the art required to make and use the claimed invention is high, and as such, one of skill in the art would recognize administration routes would not allow the virus to gain access to a particular tumor and would not use such a route; rather, they would use an administration route that provides access to the tumor. Furthermore, Applicants contend that the claims are not limited to any specific type of tumor; therefore, it would be inappropriate to narrow the claims to an administration route that is amenable to a particular tumor type when other administration routes are effective for other tumor types and determining whether a particular administration route would be effective for a particular tumor is routine for those of ordinary skill in the art.

In response, it is acknowledged that the level of skill in the art required to make and use the claimed invention is high. However, the claims encompass any route of administration wherein one or more tumor cells are infected with the HSV. It is noted that claims 6 and 8 explicitly indicated that the cancer is a noncentral nervous system cancer and claims 7 and 9

explicitly indicate that the cancer is a central nervous system cancer. Therefore, the claims encompass treating central nervous system cancers as well as non-central nervous system cancers by any administration that results in infection of tumor cells. Since the claims encompass treating the tumors by any route of administration, the claims not enabled for the full scope for the reasons of record, as indicated above. It is respectfully pointed out that the only route of administration taught by the specification which would result in the infection of tumor cells (in view of the unpredictable nature of the invention) is directly administering the HSV to the tumor by direct injection into the tumor (e.g., see Example 3, page 9, first paragraph), which is indicated as the scope the claims which is enabled. Furthermore, Applicants appear to be arguing that since the claims encompass embodiments which are enabled, one of skill in the art would recognize which embodiments are enabled and use the route(s) of administration that are enabled by the specification. However, since the claims clearly encompass embodiments which are not enabled by the specification, the rejection is appropriate. It is also respectfully pointed out that amending the claims such that the are limited to enabled embodiments would overcome the instant rejection. As indicated above, the limitation that the route of administration is one that results in one or more tumor cells being infected with the HSV does not limit the claim to direct administration of the HSV to the tumor. Therefore, applicants arguments are not persuasive and the rejection is not withdrawn.

With respect to the rejection of claims under 35 USC 102 Applicants argue that the claims have been amended such that they are now limited to treating a "patient". Furthermore, Applicants contend that because a "patient" is understood in the art as being a person (i.e.,

human) and since neither Advani reference discloses administration of HSV to a person, neither reference anticipates the present claims.

In response, it is respectfully pointed out that the specification does not appear to define the term "patient" as human or in any way that excludes mice. Since Advani clearly teaches treating mice which are suffering from cancer, the mice are patients. Furthermore, it is pointed out that the specification explicitly discloses treating mice having tumors and there are no examples disclosing the treatment of human patients. Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn.

With respect to the rejection of claims under 35 USC 103, Applicants argue that the claims have been amended such that they are now limited to treating a "patient". Furthermore, Applicants contend that because a "patient" is understood in the art as being a person (i.e., human) and since the cited references do not contemplate treating a human or suggest or provide motivation to treat a person, the rejection has failed to set forth a *prima facie* case of obviousness.

In response, it is respectfully pointed out that the specification does not appear to define the term "patient" as human or in any way that excludes mice. Since Advani clearly teaches treating mice which are suffering from cancer, the mice are patients. Furthermore, it is pointed out that the specification explicitly discloses treating mice having tumors and there are no examples disclosing the treatment of human patients. Additionally, it appears that Applicants are arguing against the references individually. In response, to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually

where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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